1,126,672

PATENT SPECIFICATION

NO DRAWINGS

1,126,672

Date of Application and filing Complete Specification: 6 Dec., 1965.

No. 51658/65.

Application made in Germany (No. F44629 IVb/12q) on 8 Dec., 1964.

Complete Specification Published: 11 Sept., 1968.

Index at acceptance:—C2 C(1J1A1, 1J1A3, 1J1A5, 1J1A7, 1J1B, 1J1C2, 1J1C3)

Int. Cl.:—C 07 c 143/80

COMPLETE SPECIFICATION

Sulphamylanthranilic Acid Amides and process for their manufacture

ERRATA

SPECIFICATION No. 1,126,672

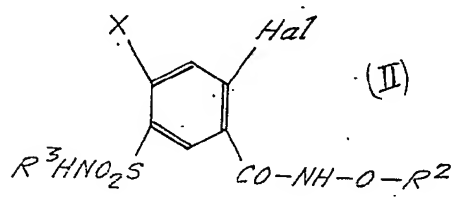
Page 2, line 67, *for* "form" *read* "from"
Page 2, line 88, *after* "by" *insert* "reacting"
Page 3, line 62, *for* "-hydroamide" *read* "-hydroxamide"
Pages 3 and 4, lines 99, 42, 85 and 87, *for* "methoxide" *read* "methoxamide"
Page 4, line 79, *after* "benzyl-" *insert* "5-"

THE PATENT OFFICE
14 October 1968

in which R^1 represents a benzyl, furfuryl or thenyl-(2) group, R^2 represents a hydrogen atom or a straight-chained or branched alkyl group containing 1 to 3 carbon atoms, R^3 represents a hydrogen atom or a methoxy group, and X represents a chlorine or bromine atom.

The present invention also provides a process for the manufacture of these new compounds, which comprises reacting

a) a dihalogeno-sulphamylbenzoic acid amide of the general formula II



II which are suitable for use according to method (a) there may be mentioned, for example: the hydroxamides, methoxamides, ethoxamides, propoxamides or isopropoxamides of the following dihalogeno - sulphamylbenzoic acids: 3 - sulphamyl - 4:6 - dichlorobenzoic acid, 3 - sulphamyl - 4:6 - dibromobenzoic acid, 3 - sulphamyl - 4 - chloro - 6-bromo - benzoic acid, 3 - sulphamyl - 4-chloro - 6 - fluoro - benzoic acid and 3 - sulphamyl - 4 - bromo - 6 - fluoro - benzoic acid. The dihalogeno - sulphamyl - benzoic acids mentioned are known compounds. For the preparation of the corresponding hydrox- or alkoxamides of sulphamylbenzoic acids of the general formula II, in which R^3 represents a hydrogen atom, the dihalogeno-sulphamylbenzoic acids mentioned are reacted at temperatures between 80° and 100°C, if desired with the addition of dioxan as diluent, with an excess of thionyl chloride, the thionyl chloride

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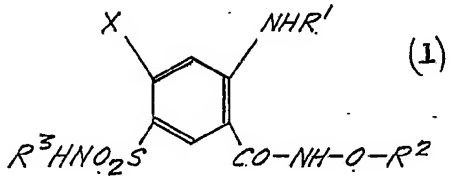
COMPLETE SPECIFICATION

Sulphamylanthranilic Acid Amides and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a Body Corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new sulphamylanthranilic acid amides and with their manufacture and use.

The present invention provides sulphamylanthranilic acid amides of the general formula I

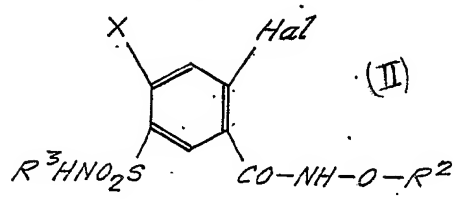


(I)

in which R^1 represents a benzyl, furfuryl or thenyl-(2) group, R^2 represents a hydrogen atom or a straight-chained or branched alkyl group containing 1 to 3 carbon atoms, R^3 represents a hydrogen atom or a methoxy group, and X represents a chlorine or bromine atom.

The present invention also provides a process for the manufacture of these new compounds, which comprises reacting

a) a dihalogeno-sulphamylbenzoic acid amide of the general formula II



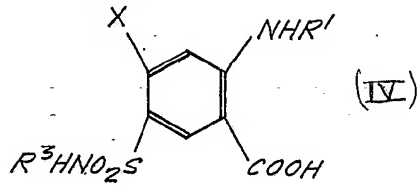
(II)

in which Hal represents a halogen atom, with an amine of the general formula III

$$NH_2R^1 \qquad (III)$$

or

b) a reactive derivative of a sulphamylanthranilic acid of the general formula IV



(IV)

with a compound of the general formula V

$$H_2N—O—R^2 \qquad (V)$$

As starting materials of the general formula II which are suitable for use according to method (a) there may be mentioned, for example: the hydroxamides, methoxamides, ethoxamides, propoxamides or isopropoxamides of the following dihalogeno - sulphamylbenzoic acids: 3 - sulphamyl - 4:6 - dichlorobenzoic acid, 3 - sulphamyl - 4:6 - dibromobenzoic acid, 3 - sulphamyl - 4 - chloro - 6-bromo - benzoic acid, 3 - sulphamyl - 4-chloro - 6 - fluoro - benzoic acid and 3 - sulphamyl - 4 - bromo - 6 - fluoro - benzoic acid. The dihalogeno - sulphamyl - benzoic acids mentioned are known compounds. For the preparation of the corresponding hydrox- or alkoxamides of sulphamylbenzoic acids of the general formula II, in which R^3 represents a hydrogen atom, the dihalogeno-sulphamylbenzoic acids mentioned are reacted at temperatures between 80° and 100°C, if desired with the addition of dioxan as diluent, with an excess of thionyl chloride, the thionyl chloride

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SEE ERRATA SLIP ATTACHED

and solvent which have not been consumed are removed by distillation *in vacuo*, and the carboxylic acid chloride which is usually obtained in an amorphous state is reacted in aqueous tetrahydrofuran, without further purification, at a temperature within the range of from 0° to 20°C, with an excess of an amine of the general formula V. It is also advantageous to carry out the reaction with an equivalent amount of the said amine in pyridine. When the reaction has been terminated, the reaction solution is, in each case, poured into dilute acetic acid and the separated amide is purified by recrystallization from a mixture of ethanol and water, from benzene or from a mixture of ethyl acetate and petroleum ether. As amines of the general formula V there may be used, for example, O-methyl-hydroxylamine, O-ethyl - hydroxylamine, O - *n* - propyl-hydroxylamine or O - isopropyl - hydroxyl-amine.

In order to obtain the starting materials of the general formula II, in which R^3 represents a methoxy group, the corresponding 3 - methoxysulphamyl - 4:6 - dihalogeno-benzoic acids are converted in the manner described above via the corresponding acid chloride into the corresponding hydrox- or alkoxamides. The preparation of these 3-alkoxysulphamyl - 4:6 - dihalogeno - benzoic acids is described in British Patent Application No. 29374/65 (Serial No. 1,108,950).

The halogen exchange reaction with the amines of the general formula III, namely benzylamine, furfuryl- and thenyl-(2)-amine, acording to method (a) is carried out at a temperature within the range of from 50° to 120°C. The temperature preferred for the exchange of a fluorine atom is within the range of from 60° to 80°C, and for the exchange of a chlorine or bromine atom within the range of from 80° to 110°C.

For complete reaction at least 2 equivalents of an amine of the general formula III are required, since 1 equivalent of hydrohalic acid must be bound. It is advantageous to use an excess of 3 to 5 equivalents of the amine, which will accelerate the reaction. Moreover, by this means the reaction mixture remains liquid and it is then not necessary to add any solvent. It is, however, also possible, especially when reacting the valuable amine components furfuryl- or thenyl - (2) - amine, to use only 1 equivalent of the base and to add a tertiary amine, for example pyridine, triethylamine or dimethylaniline, as acid-binding agent, and, if required, an inert solvent miscible with water, such, for example, as methanol, ethanol, isopropanol, tetrahydrofuran, dioxan, ethylene-glycol-monomethyl ether or diethylene-glycol-dimethyl ether. In order to be worked up the solution obtained is poured into dilute acetic acid, whereupon the final products of the general formula I usually precipitate in a crystalline state. For further purification they are advantageously recrystallized from ethanol or form a mixture of ethanol and water, if desired with the addition of charcoal.

The method (a) of the present invention is based on the surprising fact, which could not be foreseen, that a carbonamide group, which is generally not characterized by a distinct activating property, activates the halogen atom in the ortho-position to such a degree that it is exchanged easily by means of the amines mentioned, whereas the chlorine or bromine atom in the para-position is not affected.

The method described under paragraph (a) is, however, less suitable for the preparation of compounds of the general formula I in which R^2 represents a hydrogen atom, since at the reaction temperatures required for the exchange of the halogen atom some of the corresponding hydroxamides of the general formula II start to enter secondary reactions.

The compounds of the present invention may also be prepared according to the method described under paragraph (b) by reactive functional derivatives of carboxylic acids of the general formula IV with amines of the general formula V. The carboxylic acids of the general formula IV in which R^3 represents a hydrogen atom are known compounds. Those of the carboxylic acids of the general formula IV in which R^3 represents a methoxy group are described in British Patent Application No. 29374/65 (Serial No. 1,108,950). As reactive derivatives of the acids of the general formula IV there may be used, in particular, the symmetric anhydride, a mixed anhydride, the azide, activated esters such, for example, as a nitrophenyl ester, cyanomethyl ether, thiophenyl ester and N-hydroxy-phthalimido ester and, if R^1 represents a benzyl group, also the carboxylic acid chloride. Moreover, the activated intermediates can also be produced *in situ* by means of the condensing agents known from peptide chemistry, for example dicyclohexyl-carbodiimide, carbonyldiimidazole, phosphorus oxychloride, diethylchlorophosphite or tetraethylpyrophosphite.

It is particularly advantageous to use the symmetric anhydride of an acid of the general formula IV, which can be easily prepared from the corresponding acid by means of dicyclohexylcarbodiimide in tetrahydrofuran, which crystallizes well, can be stored for any period of time and gives almost quantitative yields in carbonamide.

The mixed anhydride can be prepared, for example, by reaction of the acid in question with equivalent amounts of chloroformic acid ethyl ester and triethylamine in absolute tetrahydrofuran at a temperature within the range of from −10° to 0°C, and the chloride by reaction with an excess of thionyl chloride at a temperature between 50° and 90°C. The activated esters are advantageously prepared by reacting the chloride at a temperature between 0° and 10°C in an inert solvent, in the

presence of 1 equivalent of triethylamine, with the corresponding alcohols. In order to prepare the azide the chloride is converted into the hydrazide in the usual manner and the latter is reacted at 0°C with 1 equivalent of nitrous acid.

When preparing the compounds of the present invention according to method (b) it is advantageous to introduce the reactive derivative of a carboxylic acid of the general formula IV portionwise at room temperature into a solution of excess hydroxylamine, O-methylhydroxylamine, O - ethyl - hydroxylamine, O - *n* - propyl - hydroxylamine or O - isopropyl - hydroxylamine and to complete the reaction of the chloride, the azide or the mixed anhydride at a temperature within the range of from 0° to 20°C. The reaction of the symmetric anhydride with the compound of the formula V is carried out by heating the whole for a short period of time to an elevated temperature of up to about 60°C, preferably within the range of from 30° to 50°C, until completely dissolved. The mixture is then diluted with water, its pH-value adjusted to 7.0—7.5 by means of an acid such as acetic acid, and the reaction product of the general formula I is allowed to crystallize at a lower temperature, for example at 0°C. This method of operation as well as being suitable for the symmetric anhydride starting materials, may also be applied to the corresponding carboxylic acid chloride or azide or to an activated carboxylic acid ester.

The reaction via a mixed anhydride is advantageously carried out without isolation of the said anhydride by dissolving equimolar amounts of an acid of the general formula IV and chloroformic acid ethyl ester in absolute tetrahydrofuran, adding an equimolar amount of anhydrous triethylamine at 0°C and 10 minutes after the addition has been completed, adding in one portion, also at 0°C, a base of the general formula V in an excess of 1.5 times to twice its molar amount. The whole is then allowed to react at room temperature for about one hour, the reaction solution is concentrated, diluted with water, and the final product of the general formula I is allowed to crystallize at a pH-value of 7.0—7.5.

The compounds of the present invention of the general formula I are distinguished by an excellent diuretic and saluretic activity, reduced separation of potassium and a very low toxicity. As compared with known analogous compounds of similar constitution, the compounds of the invention show the same general effect, but a considerably prolonged period of activity. The novel compounds, especially 4 - chloro - N - [2 - furfuryl] - 5-sulphamyl-methoxamide or -hydroamide, may, therefore, be used with particular advantage in the edema therapy, when careful dehydration is desired. The compounds of the invention have hypotensive properties, but may also be used in combination with hypotensively active compounds for the treatment of hypertonia.

The compounds of the invention can be administered orally as well as parenterally.

The present invention further provides pharmaceutical preparations which comprise the compounds of the general formula I in admixture or conjunction with a pharmaceutically suitable carrier. The preparations may be in the form of, for example, tablets, dragées, capsules or ampoules, advantageously in admixture or conjunction with the usual pharmaceutical carriers such, for example, as starch, lactose, tragacanth or magnesium stearate.

The following Examples illustrate the invention:

EXAMPLE 1.

4 - Chloro - N - [furfuryl] - 5 - sulphamyl-anthranilic acid methoxamide.

Into a solution of 2.0 grams of O-methylhydroxylamine in 50 cc of 50% aqueous tetrahydrofuran, 6.44 grams of the symmetric anhydride of 4 - chloro - N - [furfuryl] - 5-sulphamyl - anthranilic acid (10 mols) were introduced at room temperature, the mixture was heated for 5 minutes at 60°C, the clear reaction solution was diluted with 100 cc of water, and its pH-value was adjusted to 7.5 by means of 2N-sodium carbonate. After having been allowed to stand overnight at 0°C, the methoxide was filtered off with suction and washed with water. There were obtained colourless prisms melting at 165°C. Yield: 3.1 grams.

The 4 - chloro - N - [furfuryl] - 5 - sulphamyl-anthranilic acid anhydride used as starting material can be prepared in the following manner:

To a solution of 66.2 grams of 4-chloro-N-[furfuryl] - 5 - sulphamyl - anthranilic acid in 0.6 litre of tetrahydrofuran 41.2 grams of dicyclohexyl-carbodiimide were added. After the whole had been allowed to stand for 18 hours at room temperature the unreacted carbodiimide was decomposed by the addition of 10 cc of glacial acetic acid, the precipitated dicyclohexyl-urea was filtered off with suction, and the filtrate was concentrated by evaporation. The crystalline crude product was liberated from the by-products by boiling with 0.8 litre of ethanol, it was then dissolved in 0.2 litre of dimethylformamide while being slightly heated and reprecipitated in a crystalline state at room temperature by the portion wise addition of a total amount of 0.2 litre of water. After having been washed with dimethylformamide of 50% strength and water, the product was dried in air. Yield: 38 Grams of yellowish prisms which decomposed at 183—185°C while darkening.

EXAMPLE 2.

4 - Chloro - N - [furfuryl] - 5 - sulphamyl-anthranilic acid hydroxamide.

To a solution of 13.8 grams of hydroxylamine-hydrochloride (0.2 mol) in 40 cc of water there were added, while cooling with ice, first 40 cc of 5N-sodium hydroxide solution and then 60 cc of tetrahydrofuran. Into the mixture so obtained 12.9 grams of the symmetric anhydride of 4 - chloro - N - [furfuryl] - 5 - sulphamyl - anthranilic acid (20 millimols) were introduced at room temperature while stirring, and stirring was continued for another hour. After the reaction solution had been diluted with 0.2 litre of water and the pH-value adjusted to 7.5 by means of 2N-sodium carbonate, the hydroxamide was precipitated in a crystalline state by cooling it for several hours in ice water, and it was then recrystallized from 100 cc of water. Yield: 4.3 grams of colourless crystals which decomposed at 167°C.

EXAMPLE 3.

4 - Chloro - N - [furfuryl] - 5 - sulphamyl-anthranilic acid ethoxamide.

A mixture of 31.3 grams of 2:4 - dichloro-5 - sulphamyl - benzoic acid ethoxamide (melting point 207°C) (0.1 mol), prepared from 2:4 - dichloro - 5 - sulphamyl - benzoic acid chloride and O - ethyl - hydroxylamine, and 50 cc of furfurylamine was stirred for 1 hour at 100°C. The clear reaction solution was poured into 1.0 litre of acetic acid of 5% strength, and the condensation product which had precipitated in the solid state was recrystallized from ethanol of 50% strength, while adding charcoal. There were obtained colourless prisms melting at 194°C. Yield: 22.5 grams.

EXAMPLE 4.

4 - Chloro - N - benzyl - 5 - sulphamyl-anthranilic acid methoxide.

32.2 Grams of 4 - chloro - N - benzyl - 5-sulphamyl-anthranilic acid chloride were introduced portionwise, during the course of 15 minutes, while cooling with ice and stirring, into a solution of 15 grams of O-methyl-hydroxylamine in 0.3 litre of tetrahydrofuran of 80% strength. Immediately afterwards the mixture was concentrated to one third of its volume, 0.2 litre of water was added and the pH-value was adjusted to 7.5. The crude product which had precipitated in a crystalline state was purified by recrystallisation from a mixture of ethanol and water, while adding decolourizing charcoal. Yield: 21.8 grams; melting point: 187°C.

The 4 - chloro - N - benzyl - 5 - sulphamyl-anthranilic acid chloride used as starting material can be prepared in the following manner:

To a solution of 34.1 grams of 4-chloro-N - benzyl - 5 - sulphamyl - anthranilic acid in 100 cc of dioxan were added dropwise, at 80°C, while stirring, 20.0 cc of thionyl chloride, and stirring was continued at this temperature for 15 minutes. From the reaction solution which had been cooled to room temperature the chloride was precipitated in the form of an oil by means of 0.3 litre of petroleum ether and crystallized when triturated with further amounts of petroleum ether.

EXAMPLE 5.

4 - Chloro - N - benzyl - 5 - sulphamyl-anthranilic acid isopropoxamide.

25 Grams of O - isopropyl - hydroxylamine were reacted in the manner described in Example 4 with 32.3 grams of 4 - chloro - N-benzyl - sulphamyl - anthranilic acid chloride, and the amide was recrystallized from a mixture of ethanol and water. Yield: 22.5 grams of colourless prisms melting at 162°C.

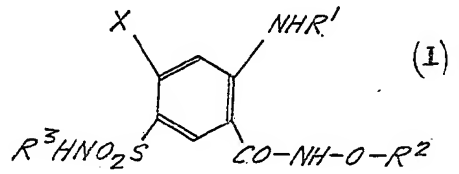
EXAMPLE 6.

4 - Chloro - N - [2 - thenyl] - 5 - sulphamyl-anthranilic acid methoxide.

28.3 Grams of 2 - fluoro - 4 - chloro - 5-sulphamyl-benzoic acid methoxide (melting point 220°C) (0.1 mol) were heated for one hour on a steam bath while stirring with 60 cc of 2-thenylamine. The reaction solution was poured into 0.6 litre of acetic acid of 10% strength. A light yellow resin separated which in the course of several hours crystallized at room temperature. For the purpose of purification the product was recrystallized from a mixture of ethanol and water, while adding decolourizing charcoal. Melting point: 168—169°C; yield: 19.0 grams.

WHAT WE CLAIM IS:—

1. A sulphamylanthranilic acid amide of the general formula I



(I)

in which R^1 represents a benzyl, furfuryl or thenyl-(2) group, R^2 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms, R^3 represents a hydrogen atom or a methoxy group and X represents a chlorine or bromine atom.

2. 4 - Chloro - N - [furfuryl] - 5 - sulphamyl - anthranilic acid methoxamide.

3. 4 - Chloro - N - [furfuryl] - 5 - sulphamyl - anthranilic acid hydroxamide.

4. 4 - Chloro - N - [furfuryl] - 5 - sulphamyl - anthranilic acid ethoxamide.

5. 4 - Chloro - N - benzyl - 5 - sulphamyl-anthranilic acid methoxamide.

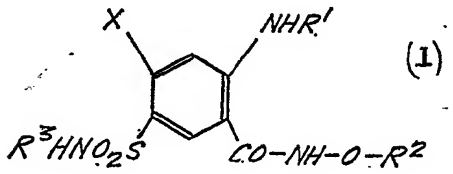
6. 4 - Chloro - N - (2 - thenyl) - 5 - sulphamyl - anthranilic acid methoxamide.

7. 4 - Chloro - N - benzyl - 5 - sulphamyl-anthranilic acid isopropoxamide.

8. A pharmaceutical preparation which comprises a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

9. A pharmaceutical preparation which comprises the compound claimed in any one of claims 2 to 7 in admixture or conjunction with a pharmaceutically suitable carrier.

10. A process for preparing a sulphamyl-anthranilic acid amide of the general formula I



(I)

in which R^1 represents a benzyl, furfuryl or thenyl-(2) group, R^2 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms, R^3 represents a hydrogen atom or a methoxy group, and X represents a chlorine or bromine atom, which comprises reacting

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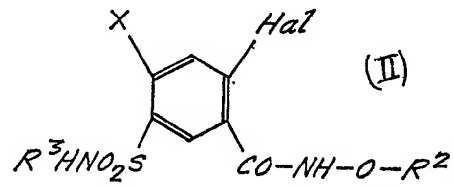
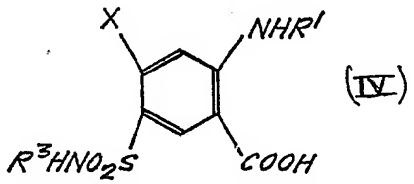


(II)

in which Hal represents a halogen atom, with an amine of the general formula III

$$NH_2R^1 \qquad (III)$$

b) a reactive derivative of a sulphamyl-anthranilic acid of the general formula IV



(IV)

with a compound of the general formula V

$$H_2N—O—R^2 \qquad (V)$$

11. A process as claimed in claim 10, and conducted substantially as described in any one of Examples 1 to 6 herein.

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